Perspectives on Cell & Gene Therapy Development, Manufacturing, and Commercialization In Japan

October 7, 2024

FIRM
Forum for Innovative Regenerative Medicine

Alliance *for* Regenerative Medicine

AliraHealth

Research Collaborators

The Forum for Innovative Regenerative Medicine (FIRM) is a Japanese general incorporated association dedicated to advancing the industrialization of regenerative medicine, including cell therapies, tissue engineering, and gene therapies, in Japan.

Established in 2011, FIRM consists of approximately 200 companies and individuals from diverse fields such as pharmaceuticals, biotechnology, manufacturing, transportation, and insurance. FIRM aims to ensure the safe and consistent delivery of regenerative medical products by collaborating closely with the Japanese government and academic institutions.

The Alliance for Regenerative Medicine (ARM) is the leading international advocacy organization championing the benefits of engineered cell therapies and genetic medicines for patients, healthcare systems, and society. As a community, ARM builds the future of medicine by convening the sector, facilitating influential exchanges on policies and practices, and advancing the narrative with data and analysis. We actively engage key stakeholders to enable the development of advanced therapies and to modernize healthcare systems so that patients benefit from durable, potentially curative treatments.
As the global voice of the sector, we represent more than 400 members across 25 countries, including emerging and established biotechnology companies, academic and medical research institutions, and patients.

Alira Health is a global healthcare firm whose mission is to humanize healthcare and life sciences in partnership with patients. From development to medical care, we complement the expertise of our pharma, biotech, medtech, and industry clients with a full spectrum of services across their entire solutions lifecycle, including clinical operations, real-world evidence, and patient-centric technology offerings.

Our integrated and multidisciplinary team of over 800 scientists, strategists, economists, clinicians, and biostatisticians collaborate across our North American, and European offices and advise 75% of the top 50 pharma and biotech companies, and 80% of the top 50 medtech companies.

Introduction and Summary of Research & Findings

Foreword

Cell and Gene Therapies (CGTs) are an exciting technological development whose applicability to health and medicine is only beginning to be understood. Patient groups, health systems, physicians, and many other stakeholders eagerly await the availability of CGTs for diseases with high unmet needs and burden.

Markets vary widely in the number of CGTs that are available. As of June 2024, more than 30 CGTs are approved in the US and more than 20 are approved in the EU. Japan lags behind the US and the EU with only 19 approved CGTs.

The Alliance for Regenerative Medicine (ARM) and the Forum for Innovative Regenerative Medicine (FIRM) are both interested in advocating for the availability of CGTs worldwide for patients who can benefit from them. Both organizations advocate for policies that support CGT access to appropriate patients.

Research Study

ARM and FIRM jointly undertook a study to better understand the gap in available CGTs in Japan as compared to the US and the EU. The study surveyed and interviewed Western pharmaceutical, biotech, and CDMO executives to understand perceived barriers to CGT development, manufacturing, and commercialization in Japan.

Phase 1

Survey of 25 Western executives on a series of development, manufacturing, and commercialization topics.

Phase 2

In-depth live interviews with 5 Western executives to elicit deeper more nuanced insights.

Note: The insights from the five executives interviewed in Phase 2 represent their unique company experiences, which may differ from those of the broader Phase 1 respondents.

Principal Findings

This research highlighted challenges and opportunities associated with CGT development in Japan. Key findings from this research identified areas for improvement while also underscoring the market's potential benefits.

1. **Japan's regulatory process is complex**, and many cell and gene therapy developers view a lack of familiarity with the process, the specificity of requirements, and lengthy overall timelines as significant barriers to entering the Japanese market. [1]
2. **Successful development and commercialization of CGTs in Japan requires on-the-ground expertise to navigate the market**. Foreign CGT developers typically partner with a Japanese pharmaceutical company or establish an affiliate or local operating company in Japan to achieve this.
3. **Smaller biotech firms, which are focused on rapid market entry for their cell and gene therapies, may be deterred by Japan's regulatory hurdles and logistical challenges** which can lead them to view Japan as a secondary or tertiary market. In contrast, large pharmaceutical companies, with their extensive resources, are well-equipped to navigate the regulatory landscape and development process in Japan.
4. **Japan offers a potentially favorable reimbursement environment**, which may benefit CGT developers. However, addressing anticipated challenges is essential as excessive delays can contribute to some developers deprioritizing the Japanese market. (In the Phase 1 survey, questions did not clearly distinguish between Japan's reimbursement and drug pricing systems.)
5. **Some CGT developers targeting rare diseases perceive less need for local manufacturing in Japan,** as they prioritize control over centralized CMC to manage risk of process failure. However, there remain opportunities for Japanese CDMOs to become trusted global partners.

1: The opening of the PMDA's Washington D.C. office in FY2024 may facilitate access to consultation services in the US.

Phase 1 Results from Biopharma Industry Research Survey

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Introduction and Summary of Phase 1 Research & Findings

Phase 1 Overview

Phase 1 of the study involved surveying 25 executives from CGT developers and CMOs worldwide. The survey aimed to understand the gap in available CGTs between Japan and the US/EU by exploring barriers to CGT development, manufacturing, and commercialization in Japan.[1]

Respondent Demographics

Twenty-five executives representing CGT developers and CMOs, ranging from 50 to more than 5,000 employees, responded to the survey. 56% had 50-500 employees, and 28% had more than 1,000. About one-third had 5 or more CGTs in development, and about half had 2 to 5 CGTs in development.

Principal Findings

Respondents highlighted a variety of benefits of the Japanese market, including that Japan has a potentially favorable reimbursement environment, and a high-quality workforce to aide in development, manufacturing, and commercialization of novel therapies. Respondents also identified several key barriers that they either encounter while developing or commercializing CGTs in Japan, or that inhibit engagement with the Japanese market. Phase 1 findings include:

1. **The Japanese regulatory process is complex to navigate and somewhat unknown to foreign drug developers**. Additionally, Japan's regulatory process emphasizes focus on safety over efficacy. Together, these pose significant hurdles for CGT development in Japan.[2]
2. **Requiring clinical trials to be conducted in Japanese patients to enable drug approval in Japan presents a significant barrier**. Recruitment challenges paired with limited budget for smaller Biotechs deters interest in early CGT development in Japan.[3]
3. **Having Japanese partners is critical for the successful development and commercialization of CGTs in Japan**, however there is low awareness of potential partners with expertise in regulatory processes, clinical development, and reimbursement.

1: See appendix for further information on research methods and objectives.; 2: The opening of the PMDA's Washington D.C. office in FY2024 may facilitate access to consultation services in the US.; 3: This requirement is only for pivotal trials for regulatory approval by PMDA, not Phase 1 clinical trials (link).

Respondent Demographics

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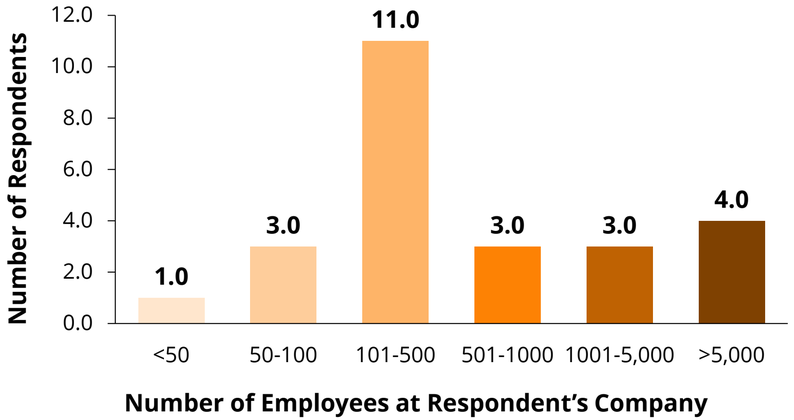
Descriptive Statistics: Company Information & Respondent Roles From Among 25 Total Survey Respondents

Size of Company



Respondent Roles

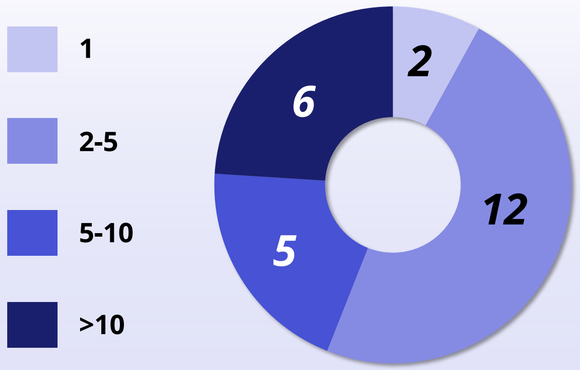
Respondent Role Within their Company	Number of Respondents[1]
Executive Leadership (C-Suite)	21
Clinical Development	11
Discovery and Preclinical Development	6
Manufacturing	6
Commercial	6
Medical	5
Fundraising and Investor Relations	3

Engagement In Japanese Market

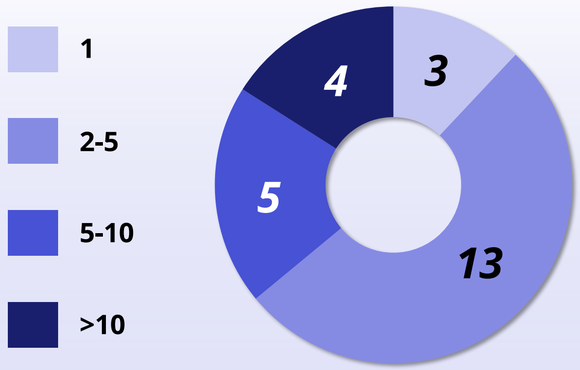
How Company is Engaged in JP Market	Number of Respondents[1]
Considering launching CGT in JP; no current plans or partnerships to do so	9
Has CGT in development with intention to launch in JP through partnership	7
Has CGT in development with intention to launch in JP independently	6
Has approved products that are commercially available in JP marketed independently	4
Has approved products that are commercially available in JP marketed through partnership	2
Has no plans to launch CGTs in Japan	2

Clinical and Commercial Stage Assets For Respondent Companies

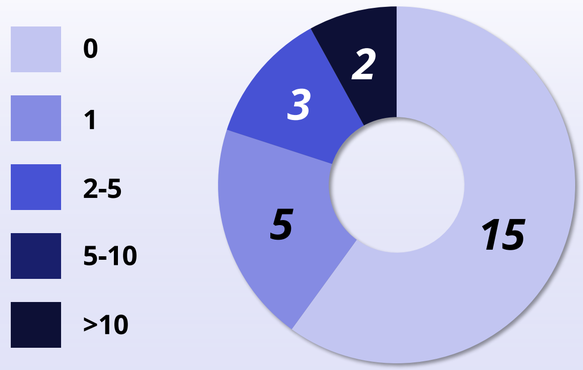
Number of Programs Currently in Development



Number of CGTs Currently in Development



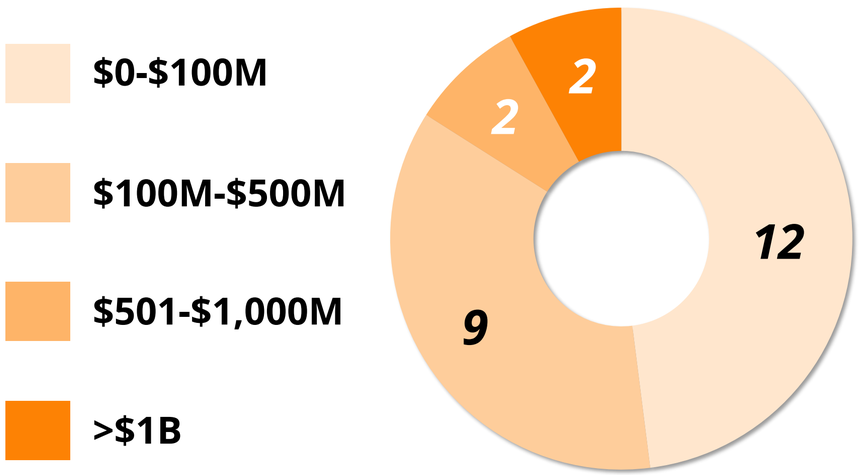
Number of Approved Therapies



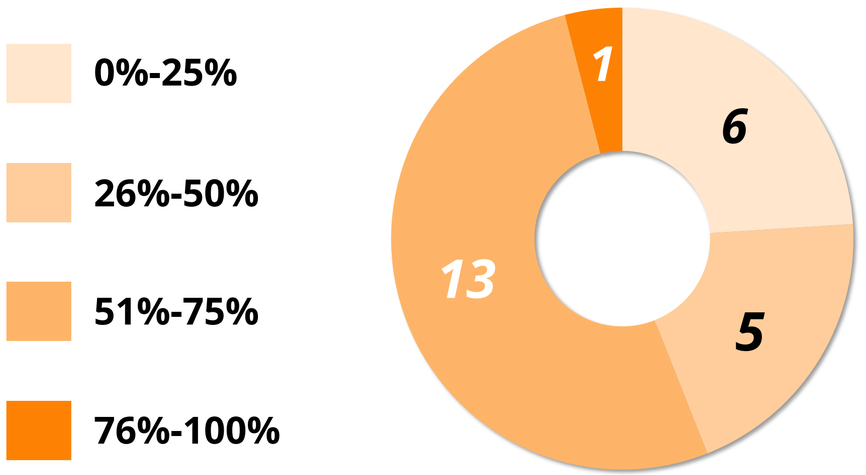
1: Respondents may select more than one option

Descriptive Statistics: R&D Budget Information From Among 25 Total Survey Respondents

Total R&D Budget of Respondents



Proportion of R&D Budget Spent on Clinical Development



How R&D Budget is Expected to Change Over the Next 3 Years	*Number of Respondents*
I expect the total budget to **significantly increase**	*4*
I expect the total budget to **increase**	*9*
I expect the total budget to **stay the same**	*9*
I expect the total budget to **decrease**	*2*
I expect the total budget to **significantly decrease**	*1*

Perceptions of Japanese Market Dynamics and Opportunity

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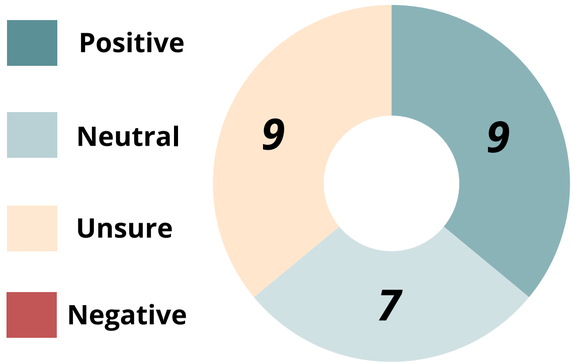
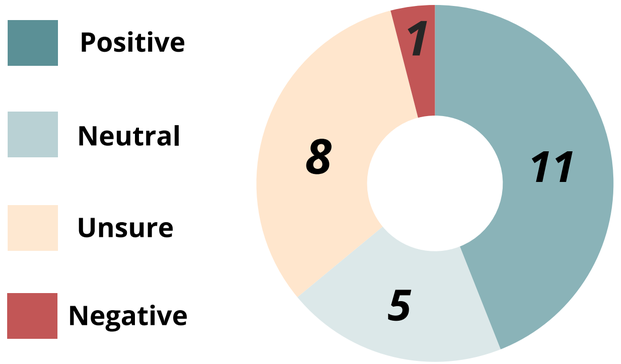
Developers Believe that Perceptions of Cell and Gene Therapies are Generally Positive or Neutral Among Patients, Caregivers, Physicians, and Regulators in Japan

Questions 17, 18, 19:
In your experience how would you characterize the perception of cell and gene therapies among patients and caregivers, physicians, and regulators in Japan?

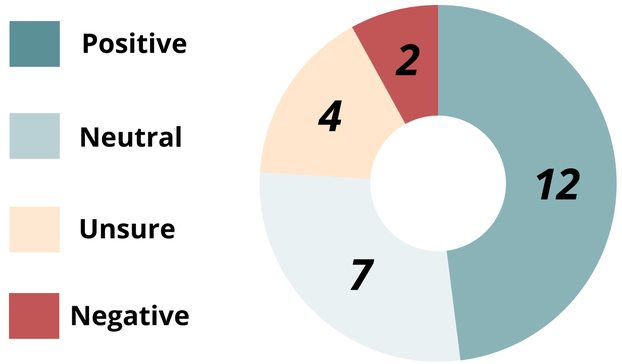
Patients and Caregivers



Physicians



Regulators



Summary of Respondent Commentary on Negative Perceptions

No respondents believe that patients and caregivers have a negative perception of cell and gene therapies

- *Among physicians in Japan, there is a general **bias toward prioritizing a drug's safety over its efficacy;** this poses a barrier as CGTs are known for their strong efficacy and potentially challenging safety profiles.*

- *The perception of adeno-associated viruses and gene editing is weak compared to cell therapies*
- *The **approval process for cell and gene therapies in Japan is longer** than in other developed markets.*
- *The extended regulatory timelines in Japan **go against de-risking efforts** for early clinical data.*

Although Most Respondents View Managing Clinical Development and Reimbursement as Similar to Other Developed Markets, Some Identify Key Challenges Associated with Drug Development in Japan

Question 16b:

Rate the attractiveness of the Japanese market based on the following factor: <u>Clinical development</u> of cell and gene therapies.

Rating Options	*Number of Respondents*
Much better than other developed markets	*0*
Better than other developed markets	*4*
Similar to other developed markets	*15*
Worse than other developed markets	*6*
Much worse than other developed markets	*0*

Challenges & Suggestions for Improvement

*"**Japan has limited critical care beds** at hospitals which are more or less required for advanced therapies. [Japan's] clinical experience with these therapies is also **less than other more developed markets leading to concerns about running clinical trials** in Japan."*
- VP, Technical Officer Cell & Gene Therapy & Biologics [CDMO]

*"**Diagnosing rare genetic disease patients** in general and finding subjects who meet the criteria to enroll in clinical studies for rare diseases and for CGTs for rare diseases is **already difficult in every country/region**, including the USA. **However, it is my perception that it is even more difficult in Japan**"*
- CEO [Biotech]

*"Global harmonization of regulatory requirements, or at least **harmonization of Japan requirements with USA or UK** would be helpful."*
- CEO [Biotech]

Question 16c:

Rate the attractiveness of the Japanese market based on the following factor: <u>Managing access and reimbursement</u> at a reasonable price for all cell and gene therapies

Rating Options	*Number of Respondents*
Much better than other developed markets	*0*
Better than other developed markets	*9*
Similar to other developed markets	*14*
Worse than other developed markets	*2*
Much worse than other developed markets	*0*

*Two respondents who believe access and reimbursement in Japan is worse than in other developed markets noted that they anticipate **reimbursement for their drug will be lower in Japan** as compared to other markets such as the US.*

The PMDA's Prioritization of Risk-Management and Safety Poses a Challenge to Developing CGTs in Japan: The Cartagena Act remains one of the barriers

Question 16a:

Rate the attractiveness of the Japanese market based on the following factor: Cell and gene therapy related regulatory processes and burden (ease of application, openness to interaction with PMDA, etc.).

Rating Options	*Number of Respondents*
Much better than other developed markets	*0*
Better than other developed markets	*5*
Similar to other developed markets	*13*
Worse than other developed markets	*7*
Much worse than other developed markets	*0*

Challenges & Suggestions for Improvement

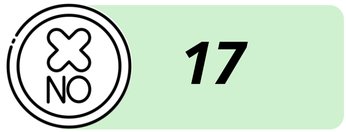
*"PMDA has always been quite conservative when it comes to risk, it would be great to see them **modernize their approach to risk.** There is a **talent gap within advanced therapies in Japan** which does affect PMDA's ability to bring experts in the space to the regulator."*
– VP, Technical Officer [CDMO]

*"The cost to manufacture cell therapies is high. Economies of scale are the one thing that help make the cost feasible long term. Most cell therapies are for orphan or ultra orphan populations. To have to incur the cost of **two manufacturing sites (costs to both license and operate)** and then not be able to have EOS come in is going to **create a financial challenge on top of an already challenging situation**."*
- CEO [Biotech]

*"The **long-term safety reporting requirements might be very challenging**. Also, the general focus on safety above all else – cell and gene (today at least) might not be the value proposition Japan is looking for in products."*
- CEO [Biotech]

Question 25:

Do regulatory frameworks such as the Cartagena Act and Japanese Standards for Biological Ingredients impact the attractiveness of developing cell and gene therapies in Japan?



*"These additional hurdles for advancing through regulatory procedures **extend development timelines**"*
- CEO [Biotech]

*"If adopted (meaning **[regulatory] process are streamlined**) will make more attractive."*
– COO & CTO [Biotech]

*"Qualification of raw materials and CMC processes can be **more complicated**"*
– Senior VP [Large Pharma]

Japan Presents an Attractive Market Opportunity Obstructed by Myriad Perceived Barriers; Seeing Examples of Commercially Successful CGTs Would Drive Interest in Launching and Marketing a Drug in Japan

Question 16d:

Rate the attractiveness of the Japanese market based on the following factor: Ability to launch cell and gene therapies.

Rating Options	*Number of Respondents*
Much better than other developed markets	*0*
Better than other developed markets	*3*
Similar to other developed markets	*18*
Worse than other developed markets	*4*
Much worse than other developed markets	*0*

Challenges & Suggestions for Improvement

*"Language [is a challenge]. **Need a local Japanese presence** for cultural reasons."*
- COO [Biotech]

*"While Japan is a large and attractive market on its own in theory, in practice it may get lumped up with a broader consideration of "how will we access Japan + China + APAC"... **most small companies would not want to have to find and manage multiple global partnerships**."*
- CEO [Biotech]

*"There have **not been very many major commercial successes** for cell and gene therapies in general, and Japan in particular, so that **reduces incentives**. I am **not aware of any/many CGTs having successfully taken advantage of the vaunted 'sakigake' pathway** to accelerate time for development and market access for their products."*
- CEO [Biotech]

*"I would be **more interested** if I better understood how cell and gene therapies are prescribed, reimbursed, and viewed **by Japanese patients**."*
- CEO [Biotech]

Question 16f:

Rate the attractiveness of the Japanese market based on the following factor: The market opportunity for cell and gene therapies.

Rating Options	*Number of Respondents*
Much better than other developed markets	*0*
Better than other developed markets	*8*
Similar to other developed markets	*12*
Worse than other developed markets	*5*
Much worse than other developed markets	*0*

Challenges & Suggestions for Improvement

*" [I] would be much more interested [in the market opportunity] if I **saw facts and figures about the growth** of CGT in Japan."*
- CEO [Biotech]

*"Japan should theoretically be one of the most attractive countries in the world for CGTs. But in practice, it feels like there are barriers to realizing that opportunity... I would love to see a major "win" involving Japan... For example: (1) A CGT company/product candidate having a **cleared CTA and first patient dosing faster in Japan** vs USA/Europe; (2) A CGT **achieving approval** at the same time or even faster in Japan vs US/Europe; (3) A CGT **commercial success in Japan**; (4) **A partnership** involving Japan early in development that **brings in meaningful and non-dilutive capital to a CGT innovator company**."*
- CEO [Biotech]

*"**Small market with limited manufacturing options** in [the] country, but many view their **aging population as attractive** because they will need more treatments."*
- VP [CDMO]

Strategic Partnership, Cultural Differences, and Barriers to Development of Cell & Gene Therapies in Japan

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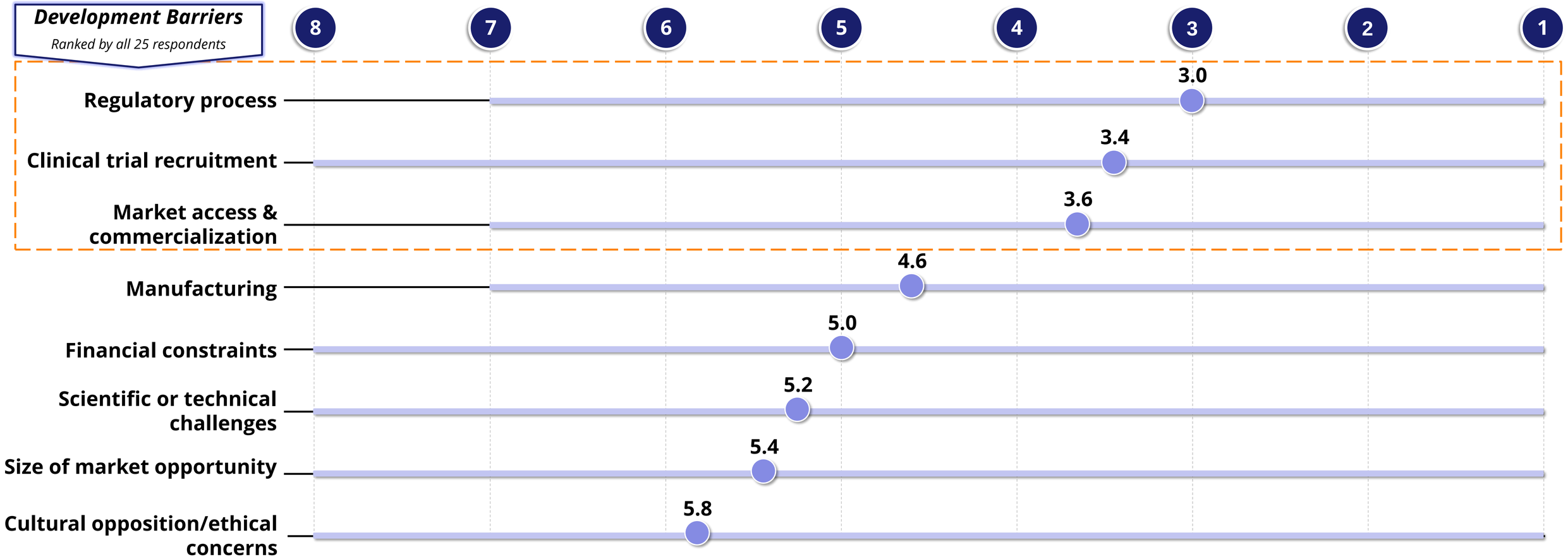
Regulatory Processes, Clinical Trial Recruitment, and Market Access & Commercialization are the Greatest Barriers To Development In Japan

Question 21:

In your opinion, what are the largest barriers to developing cell and gene therapies in Japan?



Cultural Differences in Risk Adversity along with Language Challenges Present Barriers for Small Biotechs Developing Cell and Gene Therapies

Question 26:
Do you feel that there are any cultural or language barriers to developing and marketing cell and gene therapies in Japan?

14

11

Perceived Cultural & Language Barriers

*"I don't think these are a major barrier, but for a small company there are **different cultural expectations/norms** and that would make it **challenging to set up operations** there at this point. We would **need a partner to move into this market**."*
- CEO [Biotech]

*"**Everything is very relationship driven** and it is hard to connect with [Japanese] partners."*
-CEO [Biotech]

*"We are trying to negotiate a partnership with a Japanese partner, and it has been slow (months to years). There is also **an attempt to avoid all risk, [this] doesn't mesh well with CGT biotech**."*
-CEO [Biotech]

*"Collaborating with Japanese academic or biotech is very different than western partners, e.g., [collaboration] **requires significantly more time and pre-meeting preparation**."*
- Senior Vice President [Large Pharma]

*"[Japan is] culturally a little more conservative and **balances more in favor of safety and avoiding risk**"*
-COO [Biotech]

Respondents frequently (8 mentions) cited communication and language differences as the primary barrier to developing and marketing cell and gene therapies in Japan.

Question 20:
Is there a particular stakeholder group that you believe presents as a barrier to the development, manufacturing, or commercialization of cell and gene therapies in Japan?

7

3

15 [1]

Stakeholders That Present Barriers

*"The regulatory approach is modern but **often bogged down by slow processes***
- COO/CTO [Biotech]

*"Some Japanese Companies are **more conservative** than the regulators and physicians. Important to partner in Japan for **language and cultural reasons**."*
- COO [Biotech]

*"There is a **deeper bench of biotech professionals, consultants, and CROs who are familiar with CGT requirements** in US, Canada, Europe, and Australia/New Zealand to help guide a small biotech than there are for Japan, which presents another barrier."*
-CEO [Biotech]

*"There is **more social stigma against genetic disorders, which increases barriers for patients** stepping forward and the willingness to do genetic testing and genetic counseling."*
-CEO [Biotech]

The Japanese government, regulators, and patients were all identified by respondents as stakeholders that present barriers to development in Japan.

1: Survey response option was, "Unsure/I don't know"

Japanese Partners with Clinical and Regulatory Expertise Are Needed to Help Foreign Drug Developers Comfortably Navigate Japanese Culture and Drug Development Landscape

Question 16g:

Rate the attractiveness of the Japanese market based on the following factor: The availability of strong partners to aid in the development, manufacturing and commercialization of cell and gene therapies?

Rating Options	*Number of Respondents*
Much better than other developed markets	*0*
Better than other developed markets	*4*
Similar to other developed markets	*15*
Worse than other developed markets	*6*
Much worse than other developed markets	*0*

Weaknesses and Areas for Improvement for Japanese Partners

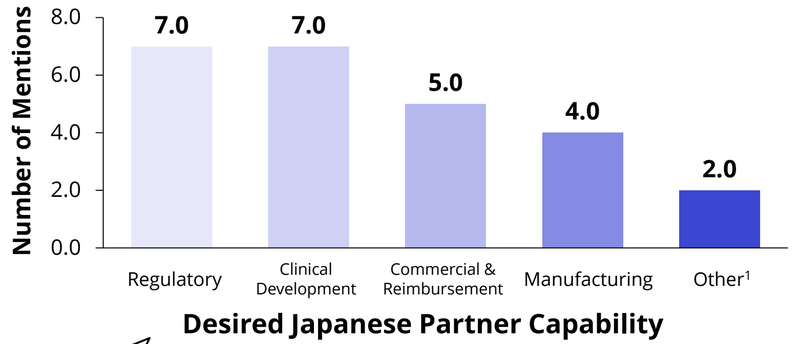
*"There are **concerns about the depth of clinical experience** and **limited options for manufacturing**. Because there are limited manufacturing options, there is a **talent gap** as well."*
- VP, Technical Officer Cell & Gene Therapy & Biologics [CDMO]

*"Most **Japanese partners do not want to be involved until programs are advanced into registrational trials**; however, that means **leaving smaller Biotechs to navigate & fund the earlier stages of development in a market where they have limited intel**. Specifically, because PMDA requires Japanese patients included in registrational trials for approval."*
-CEO [Biotech]

Question 22:

What types of partners do you need to have in Japan in order to develop, manufacture, or commercialize your therapy in Japan? What kind of capabilities are you looking for?

Potential Japanese Development Partners



Desired Japanese Partner Capability

*"Need a partner with **commercial, clinical and regulatory experience**."*
- CEO [Biotech]

*"We would need a **business development partner** to want to develop this market in order for us to **expand from the US to JPN**."*
- CEO [Biotech]

*"**On-site personnel** that can navigate the many intricacies, **nuances and differences that exist** within Japanese medical practice, regulatory, reimbursement."*
- VP, Regulatory and Scientific Affairs [Biotech]

Despite Neutral or Positive Views on the Japanese Manufacturing Workforce, Respondents Are Hesitant to Manufacture in Japan Due to Imbalance Between Investment Cost and Potential Market Opportunity

Question 16e:

Rate the attractiveness of the Japanese market based on the following factor: Ability to manufacture cell and gene therapies.

Rating Options	*Number of Respondents*
Much better than other developed markets	*0*
Better than other developed markets	*3*
Similar to other developed markets	*16*
Worse than other developed markets	*6*
Much worse than other developed markets	*0*

Challenges & Suggestions for Improvement

*"Current centralized manufacturing scheme [is] **difficult logistically** with autologous therapy."*
– VP, Regulatory and Scientific Affairs [Biotech]

*Depending on size of disease area **it may not make sense to build manufacturing for a low volume disease area**. Japan has certain specs that need exceptions to ship from other countries; local manufacturing builds do not always make sense depending on disease area.*
– CEO [Biotech]

*Limited manufacturing options other than building your own facility and there is a **steep learning curve for manufacturing staff**.*
– VP, Technical Officer Cell & Gene Therapy & Biologics [CDMO]

*3 respondents mentioned that **lack of CMOs with experience or expertise are barriers to manufacturing** in Japan.*

Question 23:

How do you perceive the quality of the Japanese workforce in the development, manufacturing, and commercialization of cell and gene therapies?

Rating Options	*Number of Respondents*
Significantly above other developed markets	*3*
Above other developed markets	*6*
Similar to other developed markets	*15*
Below other developed markets	*1*
Significantly below other developed markets	*0*

*Overall, the **majority of respondents perceive the quality of the Japanese workforce to be similar to the quality of those in other developed markets** with respect to development, manufacturing, and commercialization of CGTs. **9 respondents believe Japan's workforce is superior** in development, manufacturing, and commercialization.*

Key Areas of Support To Enable Cell & Gene Therapy Development in Japan

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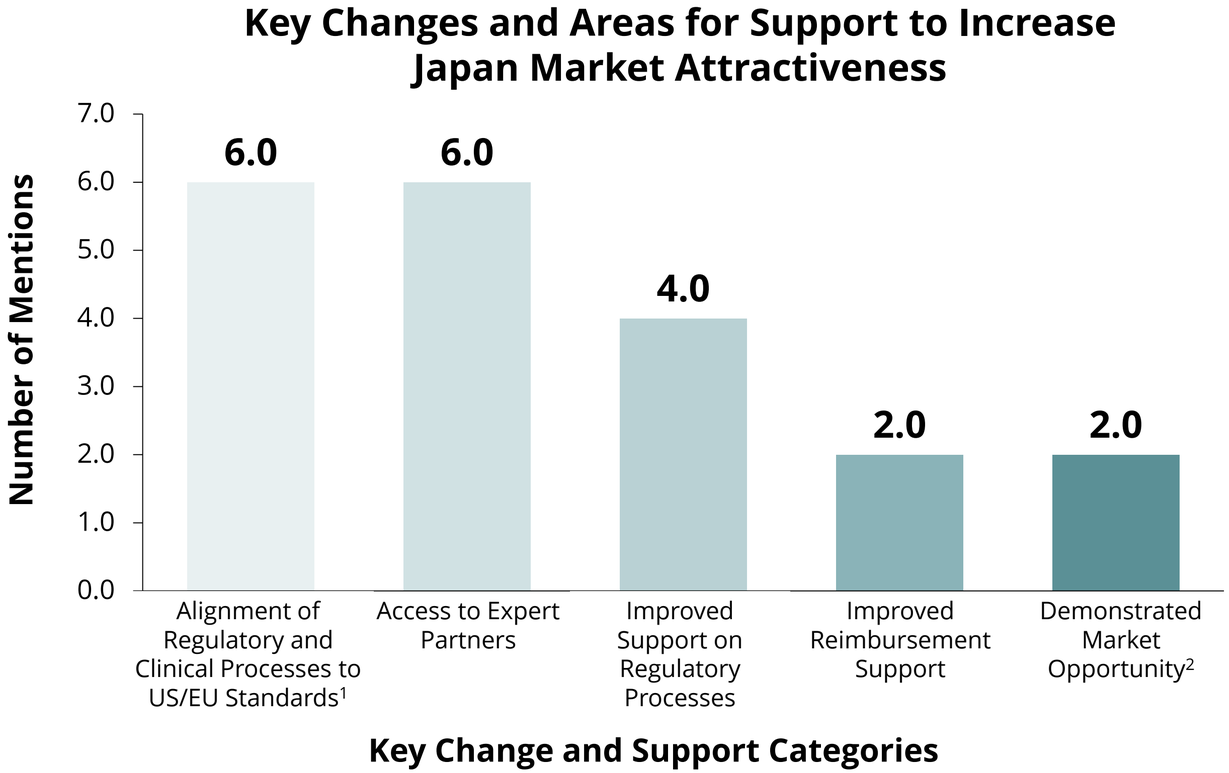
While Japan Presents a Promising Opportunity For Development of Cell and Gene Therapies, Western Drug Developers Would Like To Align the Regulatory and Clinical Processes, and Access to Expert Partners Before Pursuing Development in Japan

Question 27:
What are key changes that would make development, manufacturing, or marketing of cell and gene therapy in Japan more attractive to your company?



> *"Would **need to believe there is a vibrant market for CGT** and expectations of strong growth and a regulatory and access environment favorable to CGT"*
> - CEO [Biotech]

> ***"Allow the use of ex-Japan clinical data for registration** and for out of country manufacturing"*
> - CEO [Biotech]

> ***"Important to have local partners"***
> - Senior Vice President [Large Pharma]

> ***"Access to partners, clarity on regulatory process for [C-suite], ability to leverage US/EU clinical data…"***
> - CEO [Biotech]

> ***"Ease of converting US filings to JP** without massive rework or wait times"*
> - COO/CTO [Biotech]

1: For example, allow US trial data to support filing in Japan
2: For example, see other cases of CGTs succeeding in Japan

Phase 2 Results from Biopharma Tele-Depth Interviews

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Introduction and Summary of Phase 2 Research & Findings

Phase 2 Overview

Phase 2 of the study involved interviewing five survey respondents to gain a deeper understanding of Phase 1 findings and further explore perceived barriers to CGT development, manufacturing, and commercialization in Japan.

Respondent Demographics

Five executives from pharma and biotech companies based in the US, EU and Australia were interviewed virtually.

Three respondents work at companies with 101-500 employees, one works at a company with 501-5,000 employees, and one works at a company with more than 5,000 employees.

One company has an approved product in Japan, three companies are intending to launch in Japan through partnerships, and one company is considering launching in Japan in the future.

Principal Findings

1. **Japan's regulatory process is complex and has a long timeline, sometimes making it a secondary or tertiary market for CGT development**, particularly for biotech companies that prioritize fast-to market approaches due to limited resources. Large pharmaceutical companies, with their extensive experience and resources, are better equipped to navigate the regulatory challenges, highlighting key differences in market approach between large pharma and biotech firms.
2. **A holistic partnership with a company or affiliate based in Japan with expertise in relevant therapeutic areas and Japanese regulatory processes is highly advantageous for developing in Japan.** Large pharma companies may have existing operations in Japan and find establishing partnership to be less of a barrier than smaller biotechs.
3. **For some CGT developers, limited demand and focus on controlling centralized manufacturing may reduce need to manufacture in Japan**. However, insights from five interviews with focus on limited modalities and rare disease populations may not fully reflect the broader range of opinions on CGT development in Japan. Opportunities remain for Japanese CDMOs to become trusted local and global partners.
4. **As with other ex-US regions, one-time therapy pricing, and currency value fluctuation may pose challenges.** Respondents foresee some challenges related to pricing and market access that should be addressed to facilitate streamlined commercialization; there is a perception that Japan follows global market pricing trends for novel therapeutics, but as with other ex-US regions, one-time therapy pricing, and currency value fluctuation may pose challenges.

Japan Is a Highly Attractive Market Globally and Within the APAC Region; Although, Key Barriers to Entry Exist

Pricing & Access

Japan's relatively high reimbursement rates compared to other APAC countries make it financially attractive.

The regulatory environment, while demanding, provides a clear pathway to accessing the market.

Healthcare System

Japan has a highly developed healthcare system and established infrastructure which supports development and adoption of innovative therapies.

Market Opportunity

Japan's population is aging and has a high incidence of rare and genetic diseases, creating a substantial market for specialty cell and gene therapies.

Intellectual Property

Japan is recognized for its strong intellectual property framework and high level of trustworthiness, distinguishing it from other global markets where IP issues are more prevalent.

Large Pharma vs. Biotech

- Japan is an overall attractive market opportunity for developers of cell and gene therapies.
- Large pharma companies are better equipped to navigate complexities in the Japanese system and have existing affiliates and partner networks with on-the-ground experts to support development.
- Early-stage biotechs prioritize fast-to-market approaches in their business models. Japan is an attractive market, but length of regulatory processes is perceived as a barrier.

The Regulatory Process in Japan Is Long and Onerous, Especially for Early-Stage Biotechs With Limited Time and Resources

Regulatory Timeline Challenges

Recruiting and treating Japanese patients can be managed, but the associated costs and complexities, especially for CGTs requiring patient-derived cells, present substantial challenges and take extra time.

The process for GMO approval, particularly for AAV vectors, is lengthy even in circumstances when evidence demonstrates minimal final AAV presence in the body.

Stringent requirements and higher evidence thresholds for gene editing and *in vivo* therapeutics contribute to extended approval timelines.

Japan's rigorous safety and risk management standards, while not viewed as negative, contribute to the overall complexity and length of the approval process.

Impact on CGT Development in Japan

The extended development timeline in Japan can make it a secondary or tertiary market for CGT developers, influencing their global development priorities and delaying market entry

Large Pharma

- Large pharma, with its established infrastructure and greater financial resources, can more effectively manage the prolonged development timelines in Japan.
- Navigating complex regulation among other challenges still poses a barrier that impacts global development strategy and market prioritization.

Biotech

- The regulatory timeline in Japan poses a significant hurdle for biotechs, which rely on quick, iterative development cycles and often operate with limited time and resources.
- The delayed approval process disrupts biotechs' ability to rapidly bring CGTs to market and may jeopardize competitive edge and financial stability.

Biotech firms, which have historically driven CGT development, face significant barriers to developing in Japan, leading to CGT lag in Japan. With large pharma increasingly engaged in CGT development, their resources may accelerate the introduction of innovative CGTs to the Japanese market.

An Expert Partner or Affiliate with Existing Operations Localized in Japan Is Essential for Developing and Commercializing Cell and Gene Therapies in Japan

Key Partnership Considerations

Expertise
Japanese partners must have expertise in the therapeutic area of interest, CGTs, and operating locally in Japan. For early-stage biotech companies, local partners are preferred over US-based companies with operations in Japan.

Language and Cultural Fit
Limiting language barriers and assuring company culture compatibility are important. Effective and efficient communication and two-way trust between the developer and partner is necessary.

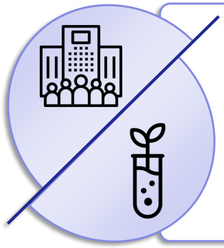
Respondents noted that translating during business meetings can greatly extend the length of communications, significantly hindering processes and efficiency.

Regulatory Navigation
Partners should be able to manage regulatory submissions, translating US or EU filings to the Japanese regulatory framework. Partners should also be able to offer support on clinical development and commercialization.

Supporting Beyond Japan
A partner that can support the expansion of development and commercialization across the APAC region to countries like China, South Korea, or Singapore is highly advantageous.

Respondents emphasized that Japan's CGT regulatory process requires a unique approach due to distinct standards and safety requirements. Partners with expertise in translating filings from other systems to Japan's are highly preferred.

Large Pharma vs. Biotech



- Partnerships are an additional financial and logistical burden to small biotechs who have limited funding and runway; large pharmaceutical companies may have existing affiliations or capital to partner in Japan.
- The need for local partnerships poses a functional challenge unique to Japan, unlike other ex-US regions where partnerships are not necessary. This hurdle is one of the most significant barriers for biotechs entering Japan.

For CGT Developers, Controlling Manufacturing to Mitigate Risk Is Crucial; Successful Partners Are Those With a Proven Track Record of Providing CMC Services Without Issues or Delays

Respondents noted limited value in expanding manufacturing capabilities to Japan, citing low product volumes and a preference to control production due to associated risks. These findings, based on five interviews, are limited to specific modalities and disease populations and may not reflect the broader spectrum of views on CGT development in Japan.

Key Limitations

- **Product demand for CGTs targeting rare diseases is viewed as limited**, with centralized manufacturing capabilities being sufficient to meet relatively modest needs. **Global distribution is not seen as a major obstacle**.
- **Manufacturing CGTs is highly complex and poses one of the greatest risks to successful commercialization of CGTs**. Respondents preferred to maintain in-house CMC capabilities as **outsourcing manufacturing to CDMOs introduces undue risk** of process failure.
- While large pharma may be more likely to invest in manufacturing capabilities or partnerships in Japan, **some early-stage biotechs may choose not to spend resources to access or operate manufacturing facilities abroad.**

Opportunities for CMC in Japan

- **Developers targeting larger indications with high-volume CGT product needs,** such as those in oncology, may have a stronger case for establishing local manufacturing in Japan, **when speed of production is more important**.
- For developers targeting rare diseases, conducting fill-finish operations in Japan provides opportunity for partnership.
- While IP confidentiality and CMC control risks can limit CDMO use outside the US, **Japan's strong IP protection offers a chance for local CDMOs to become trusted partners** for global CGT developers expanding to the APAC region.
- **Demonstrating robust capabilities is essential** for Japanese CDMOs to establish themselves as valued partners for CGT development in Japan and globally.

Respondents emphasized that Japan does not lack manufacturing opportunities; low product volume demand and risk management in rare disease CGT development are the main drivers for some respondents' lack of urgency to establish manufacturing operations in Japan.

Drug Pricing and Market Access Are Seen As Manageable Barriers for Companies Considering Development in Japan

There is a perception that Japan follows global market pricing trends for novel therapeutics, but as with other ex-US regions, one-time therapy pricing, and currency value fluctuation may pose challenges.

⊕ *Pricing Strengths*

- ✓ Japan's demonstrated willingness to pay for effective therapies drives interest in developing in Japan and does not pose a limitation or hurdle.
- ✓ Japan's advanced scientific community and healthcare infrastructure support the introduction of novel therapeutics which can lead to favorable pricing outcomes.

⊖ *Pricing Challenges*

- ✗ The process for gaining reimbursement approval can be lengthy and cumbersome, which may impact the overall market entry timeline and the ability to set optimal pricing.
- ✗ Negotiating price adjustments post-marketing is challenging in Japan. Setting an optimal initial price is crucial especially in the context of yen value fluctuation. Respondents mentioned needing to set a higher price in Japan due to yen devaluation.
- ✗ Developers of CGTs "anticipate" that negotiating pricing for a one-time therapy will be challenging and have experienced similar roadblocks in other ex-US regions.

Although price negotiations are not the largest obstacle to entering the Japanese market, addressing the identified challenges is crucial to streamline the commercialization process, as excessive delays contribute to market deprioritization.

Appendix

FIRM Forum for Innovative Regenerative Medicine
Alliance for Regenerative Medicine
AliraHealth

Phase 1 Research Survey: Objectives & Methodology

Objectives

- Investigate the causes of drug lag related to CGT products (cell therapy, tissue engineering, ex vivo gene therapy, and in vivo gene therapy, etc.) in Japan vs. US and EU
- Determine the reasons behind the lack of drug development in Japan
- Understand the criteria necessary to attract interest in manufacturing of CGT products in the APAC region, especially in Japan

Methodology

- Alira Health worked with FIRM to develop a comprehensive survey regarding standings and sentiments on developing CGTs in Japan
- Alira Health worked with ARM to identify and distribute the survey to key decision makers within pharma and biotech companies developing CGTs
- Alira Health aggregated results from 25 survey respondents; all results from quantitative and qualitative questions are included in this report

Following review of all survey results, 5 tele-depth interviews were conducted with subject matter experts to further inform this research.